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REVIEW ARTICLE

Overdose of Drugs for Attention-Deficit Hyperactivity Disorder: Clinical Presentation, Mechanisms of Toxicity, and Management

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Abstract The prevalence of attention-deficit hyperactivity disorder (ADHD) in the USA is estimated at approximately 4–9 % in children and 4 % in adults. It is estimated that prescriptions for ADHD medications are written for more than 2.7 million children per year. In 2010, US poison centers reported 17,000 human exposures to ADHD medications, with 80 % occurring in children <19 years old and 20 % in adults. The drugs used for the treatment of ADHD are diverse but can be roughly separated into two groups: the stimulants such as amphetamine, methylphenidate, and modafinil; and the non-stimulants such as atomoxetine, guanfacine, and clonidine. This review focuses on mechanisms of toxicity after overdose with ADHD medications, clinical effects from overdose, and management. Amphetamine, dextroamphetamine, and methylphenidate act as substrates for the cellular monoamine transporter, especially the dopamine transporter (DAT) and less so the norepinephrine (NET) and serotonin transporter. The mechanism of toxicity is primarily related to excessive extracellular dopamine, norepinephrine, and serotonin. The primary clinical syndrome involves prominent neurological and cardiovascular effects, but secondary complications can involve renal, muscle, pulmonary, and gastrointestinal (GI) effects. In overdose, the patient may present with mydriasis, tremor, agitation, hyperreflexia, combative behavior, confusion, hallucinations, delirium, anxiety, paranoia, movement disorders, and seizures. The management of amphetamine, dextroamphetamine, and methylphenidate overdose is largely supportive, with a focus on interruption of the sympathomimetic syndrome with judicious use of benzodiazepines. In cases where agitation, delirium, and movement disorders are unresponsive to benzodiazepines, second-line therapies include antipsychotics such as ziprasidone or haloperidol, central alpha-adrenoreceptor agonists such as dexmedetomidine, or propofol. Modafinil is not US FDA approved for treatment of ADHD; however, it has been shown to improve ADHD signs and symptoms and has been used as an off-label pharmaceutical for this diagnosis in both adults and children. The mechanism of action of modafinil is complex and not fully understood. It is known to cause an increase in extracellular concentrations of dopamine, norepinephrine, and serotonin in the neocortex. Overdose with modafinil is generally of moderate severity, with reported ingestions of doses up to 8 g. The most common neurological effects include increased anxiety, agitation, headache, dizziness, insomnia, tremors, and dystonia. The management of modafinil overdose is largely supportive, with a focus on sedation, and control of dyskinesias and blood pressure. Atomoxetine is a selective presynaptic norepinephrine transporter inhibitor. The clinical presentation after overdose with atomoxetine has generally been mild. The primary effects have been drowsiness, agitation, hyperactivity, GI upset, tremor, hyperreflexia, tachycardia hypertension, and seizure. The management of atomoxetine overdose is largely supportive, with a focus on sedation,

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and control of dyskinesias and seizures. Clonidine is a synthetic imidazole derivative with both central and peripheral alpha-adrenergic agonist actions. The primary clinical syndrome involves prominent neurological and cardiovascular effects, with the most commonly reported features of depressed sensorium, bradycardia, and hypotension. While clonidine is an anti-hypertensive medication, a paradoxical hypertension may occur early with overdose. The clinical syndrome after overdose of guanfacine may be mixed depending on central or peripheral alpha-adrenoreceptor effects. Initial clinical effects may be drowsiness, lethargy, dry mouth, and diaphoresis. Cardiovascular effects may depend on time post-ingestion and may present as hypotension or hypertension. The management of guanfacine overdose is largely supportive, with a focus on support of blood pressure. Overdose with ADHD medications can produce major morbidity, with many cases requiring intensive care medicine and prolonged hospital stays. However, fatalities are rare with appropriate care.

1 Introduction

The prevalence of attention-deficit hyperactivity disorder (ADHD) in the USA is estimated at approximately 4–9 % in children and 4 % in adults [1, 2]. It is estimated that ADHD medications are prescribed annually for more than 2.7 million children in the USA [3, 4]; the number of adults taking these medications is not clear. Over recent years, the number of prescriptions provided for medication for ADHD has increased [4, 5]. Similar to trends seen with poisoning from other pharmaceuticals, such as that seen historically with cyclic antidepressants and more recently with opioids, the wider availability of prescription ADHD medications may partially explain the increase in abuse and overdoses seen in adolescents with these medications [6]. Additionally, it has been suggested that children with ADHD are at increased risk of hospitalization from pharmaceutical ingestion [7]. In younger children, these overdoses may be unintentional events from exploratory behavior [8]; however, in adolescents, the increased availability of ADHD medication has matched increases in reports of abuse and misuse of ADHD medications [5]. Taken together, the outcome is that unintentional and intentional overdoses with ADHD medication are likely to remain common. In 2010, US poison centers reported 17,000 human exposures to ADHD medications, with 80 % occurring in children <19 years old and 20 % occurring in adults, the majority of which can be expected to have had at least some negative clinical effects [9]. Although most of these exposures are unintentional owing to the number of pediatric exploratory ingestions, thousands of exposures per year are attributed to intentional abuse, including suicide attempts and drug abuse [9].

The drugs used for the treatment of ADHD are diverse but can be roughly separated into two groups: the stimulants such as amphetamine, methylphenidate, and modafinil; and the non-stimulants such as atomoxetine, guanfacine, and clonidine [10]. This review focuses on mechanisms of toxicity after overdose with ADHD medications, clinical effects from overdose, and management. The adverse events associated with long-term therapeutic use of these agents are not covered.

2 Stimulants

2.1 Amphetamines

Amphetamine is the common name for the racemic mixture of β-phenylisopropylamine or α-methylphenylethylamine [11]. Substitutions of the phenylethylamine result in the creation of different amphetamine analogs, which are also described using the term ‘amphetamines’. Currently available prescription amphetamines include amphetamine, lisdexamphetamine, phentermine, phendimetrazine, and dextroamphetamine. Because lisdexamphetamine is rapidly converted to dextroamphetamine in the blood, it is reviewed in this section.

2.1.1 Pharmacokinetics

Amphetamines are well absorbed by all routes of administration. They are readily absorbed orally, with no significant delay from the presence of food [12]. Peak plasma concentrations are attained within 2–3 h after oral ingestion of immediate-release formulations, and within 30 min after intravenous or intramuscular injection [13]. Amphetamines are relatively lipophilic, enabling them to readily cross the blood-brain barrier [14]. They are weak bases with a pKa (logarithmic acid disassociation constant) of approximately 9.9. With a volume of distribution of 3–5 L/kg, amphetamines are widely distributed across all tissues; CSF values are approximately 80 % of plasma levels at steady state and they may accumulate in tissues or matrices with a more acidic pH than that of blood [15, 16]. Amphetamines are hepatically and renally eliminated, with approximately 30 % of a dose of amphetamines excreted unchanged [17]. Renal excretion is significantly influenced by urine pH; the excretion rate of unchanged amphetamine with urine pH of 6.6 averages 70 % versus 17–43 % in a urine with a pH of greater than 6.7 [15]. Plasma half-life is influenced by the renal elimination; the range is from 7 to 14 h with urine pH of less than 6.6 and up to 34 h for urine pH greater than 6.7 [15].

Lisdexamphetamine is a prodrug that is rapidly absorbed and is cleaved to release the active dextroamphetamine by red blood cell hydrolysis. This cleavage yields dextroamphetamine and l-lysine. No hepatic metabolism of lisdexamphetamine through the cytochrome P450 (CYP) occurs [18–20]. Peak plasma concentrations of lisdexamphetamine and dextroamphetamine occur approximately 1 and 3.5 h after oral administration, respectively [19]. Lisdexamphetamine is essentially undetectable in the plasma after 8 h, and approximately 2 % of a dose is eliminated unchanged in the urine [19]. The plasma elimination half-life is less than 1 h [19–21].

2.1.2 Mechanism of Toxicity

The mechanism of toxicity of amphetamines is primarily related to excessive extracellular dopamine, norepinephrine, and serotonin [22, 23]. The most prominent clinical picture is alpha- and beta-adrenoreceptor-mediated sympathomimetic syndrome, with psychiatric symptoms and hyperthermia secondary to the dopamine and serotonin excess [23–26].

Amphetamine and dextroamphetamine act as substrates for the cellular monoamine transporter, especially the dopamine transporter (DAT) and less so the norepinephrine (NET) and serotonin transporter [16]. They are actively taken up into the neuron via the cellular monoamine transporter, displacing monoamine stores and promoting the counter-flow release of monoamines in the brain [27]. Amphetamines cause a reversal of the uptake transporter-mediated flow, resulting in a release of monoamines. Amphetamines cause excessive synaptic neurotransmitter concentration by inhibition of monoamine reuptake via direct drug–neurotransmitter competition for the transporter and stimulation of the transporter to act as a reverse carrier.

The toxicity of lisdexamphetamine depends on the timing of the release of free dextroamphetamine.

2.1.3 Overdose

Overdoses with amphetamine have been reported since its availability and continue to remain common [9, 28]. The primary clinical syndrome involves prominent neurological and cardiovascular effects, but secondary complications can involve renal, musculoskeletal, pulmonary, and gastrointestinal (GI) effects. In overdose, the patient may present with mydriasis, tremor, agitation, hyperreflexia, combative behavior, confusion, hallucinations, delirium, anxiety, paranoia, movement disorders, and seizures [28–35]. In rare cases, seizures may progress to status epilepticus [36]. Coma may occur secondary to post ictal state, intrinsic catecholamine depletion, ischemic stroke, or intracerebral hemorrhage [37]. Hyperthermia may occur with or without seizures [31]. Rhabdomyolysis may occur as a sequelae of amphetamine-induced seizures, with associated risk of renal failure [29]. Prominent cardiovascular effects after overdose include tachycardia, hypertension, and dysrhythmias [32]. Less common effects may include aortic dissection, vasospasm, cerebral vasculitis, with subsequent intracerebral hemorrhage and myocardial infarction [38–45]. Late-stage refractory hypotension may occur in the presence of seizures, hyperthermia dysrhythmias, and acidosis. Other effects with large overdoses may include tachypnea, metabolic acidosis, and GI ischemia.

History may indicate periods of one or more days of insomnia after large overdoses or prolonged use (binges). While seizures and cardiovascular toxicity are less common than seen after intoxication with other sympathomimetic agents such as cocaine, behavioral and psychiatric effects, such as hallucinations and psychosis, are common and may be related to the more potent dopaminergic effects of amphetamines [23, 46–48]. While significant morbidity is common, fatalities are less common than with other drugs of abuse [49].

There have been no cases of lisdexaphetamine overdose reported; however, as a pro-drug of dextroamphetamine, overdose is likely to present similar to that with dextroamphetamine. The rate-limiting step of conversion to dextroamphetamine may produce a delay in onset of several hours. The LD50 (lethal dose in 50 % of test animals) of lisdexamphetamine in rats is five times that of dextroamphetamine; however, it is unclear if this will translate to similar differences in humans after overdose [50].

2.1.4 Management

The management of amphetamine (including lisdexamphetamine) overdose is largely supportive, with a focus on interruption of the sympathomimetic syndrome with judicious use of benzodiazepines.

The role of GI decontamination is limited in amphetamine overdose. Activated charcoal (AC) is known to bind to amphetamines, and some advocate its use if the patient presents early after an acute oral overdose (less than 1–2 h); however, many patients do not present within this time frame [51, 52]. Additionally, use of AC should be avoided in patients with significant risk of aspiration in whom the airway is not protected, such as those with mental status changes (CNS depression or significant agitation), or those whose clinical condition is expected to rapidly deteriorate or mandate large doses of benzodiazepines for sedation [51, 52]. Although there is limited evidence and no well established time frame, many clinicians recognize that several scenarios, including poisoning with sustained-release preparations, the presence of food in the stomach, and co-ingestion of drugs that slow GI motility

(opioids, anticholinergics) may increase GI transit time, and therefore extend the time frame during which AC could be expected to adsorb amphetamine in these patients. Additionally, onset of neurological effects such as agitation, delirium, combative behavior, or seizures may make it difficult to administer. Cautious judgment should be used when deciding whether to use this option. AC can be given in doses of 1 g/kg of body weight in adult and pediatric patients [11]. For ease of administration, AC is generally given in 50 or 100 g doses to adult patients [11].

Although previously advocated, enhancing amphetamine excretion via urine acidification is no longer recommended due to lack of effects on amphetamine toxicity and potential compromises in overall patient management (systemic acidosis, renal effects from rhabdomyolysis) [29, 53].

Amphetamine toxicity is a clinical diagnosis. Serum amphetamine concentrations are rarely available in a timely manner, and therefore are of limited clinical usefulness and not recommended unless needed for medico-legal circumstances. The differential diagnosis involves conditions producing a sympathomimetic syndrome including sepsis, encephalitis, thyrotoxicosis, or other sympathomimetic drugs.

Intravenous benzodiazepines are first-line agents following amphetamine overdose for agitation, movement disorders, seizures, tachycardia, and hypertension. Doses should be titrated to response, beginning with low doses and escalating judiciously. Large doses may be required. If intravenous access is unattainable due to agitation, combative behavior, or delirium, intramuscular administration of benzodiazepines or ketamine is recommended until intravenous access can be established [54–56]. In cases where agitation, delirium, and movement disorders are unresponsive to benzodiazepines, some authors recommend use of antipsychotics, such as ziprasidone and haloperidol [57–60]. Significant caution should be exercised if using antipsychotic medications as they can impair heat dissipation, lower the seizure threshold, and precipitate cardiac dysrhythmias, all of which may worsen clinical outcomes related to toxicity of co-ingestants, including other stimulants (cocaine) and ethanol withdrawal [23, 54, 61, 62]. Dexmedetomidine (Precedex®), a central alpha-2 adrenoreceptor agonist sometimes used for refractory amphetamine-induced agitation, may have an additional advantage in that it can mitigate the tachycardia and hypertension often seen in these patients [63–65]. Seizures resistant to benzodiazepines may respond to barbiturates, or require escalation of care, including endotracheal intubation and initiation of a barbiturate or propofol infusion. Status epilepticus should be treated in the usual fashion and may require advancement to general anesthetic sedation.

Hyperthermia should be treated emergently with external cooling and benzodiazepines. Paralysis and mechanical ventilation may be required [66]. Rhabdomyolysis can be seen in patients with severe amphetamine intoxication and is precipitated by a combination of factors, including psychomotor agitation, hyperthermia, and seizures. Rhabdomyolysis should be treated in the usual fashion, which may vary from institution to institution; however, clinicians should be mindful that urinary alkalinization may theoretically decrease elimination of amphetamines [67, 68].

The most common dysrhythmia seen is a sinus tachycardia, which alone usually does not require intervention. Hypertension and tachycardia usually respond to adequate sedation with benzodiazepines or, if needed, intravenous dexmedetomidine [63–65]. Hypertension unresponsive to benzodiazepines or alpha-adrenoreceptor agonists may require a direct vasodilator such as nitroprusside. Beta-adrenergic antagonists, such as propranolol, are generally not recommended. Although they have been used without ill effects, beta-adrenergic antagonists may result in unopposed peripheral alpha-adrenergic stimulation with resultant vasoconstriction and hypertension. In rare cases, hypertension, vasospasm, and tachycardia may result in intracerebral or subarachnoid hemorrhage, which should be treated in the usual fashion, with control of severe hypertension and surgical intervention when indicated.

2.2 Methylphenidate

2.2.1 Pharmacokinetics

Methylphenidate is well absorbed orally, with food delaying the early peak absorption by approximately 1 h [69]. There is some inter-patient variability in absorption with extended-release formulations [70]. Immediate-release formulations have a time to peak plasma concentration of 1–3 h, with an onset of action that may be as rapid as 20 min after administration [69]. Extended-release formulations vary between manufacturers, and may reach mean peak plasma concentrations between 5–10 h [71] and 1.3–8 h [72]. It should be noted that abuse of extended-release formulations via injection or by crushing and insufflation will alter the pharmacokinetics of the drug, with patients instead obtaining peak plasma concentrations more rapidly, as is seen after intravenous injection and insufflation of other drugs. Methylphenidate is hepatically metabolized, with less than 1 % of unchanged drug excreted renally, and 1–3 % in the feces [72]. Ethanol co-ingestion increases the peak plasma concentration and area under the curve of the active metabolite, but the toxicologic significance of this is currently unknown [73].

2.2.2 Mechanism of Toxicity

Methylphenidate acts as a substrate for the cellular monoamine transporter, especially the DAT and less so the

NET [74]. Methylphenidate has been shown to occupy and block the DAT, while dexmethylphenidate additionally elicits a reverse transport [74]. The actions of methylphenidate are multiple, including blockade of the DAT and NET, disinhibition of D2 autoreceptors on presynaptic dopaminergic neurons, and activation of D1 receptors on postsynaptic neurons [74]. These actions cause an increase in synaptic concentration of dopamine and norepinephrine, acting as an indirect catecholaminergic agonist. The mechanism of toxicity is primarily related to excessive extracellular dopamine and norepinephrine [22, 23]. The most prominent clinical picture is the alpha- and beta-adrenoreceptor-mediated sympathomimetic syndrome.

2.2.3 Overdose

Overdose of methylphenidate may be unintentional (e.g. young children) or intentional due to drug abuse, misuse, or intended self-harm [75, 76]. The primary clinical syndrome follows a sympathomimetic overdrive with prominent neurological and cardiovascular effects. In overdose, the patient may present with mydriasis, agitation, anxiety, tremor, hyperreflexia, confusion, hallucinations, delirium, paranoia, movement disorders, and seizures. The majority of methylphenidate overdoses have presented with moderate severity, but fatalities have been reported [75–77]. Seizures have been rare [23]. Cardiac effects are primarily sinus tachycardia and hypertension. Patients may complain of chest pain and palpitations. Methylphenidate does not appear to have substantial effects on QRS or QT intervals [78]. Neurological and cardiac effects secondary to a vasculitis or arteritis have been hemiplegia, intracerebral hemorrhage, and myocardial infarction [79, 80]. In severe cases, multi-organ failure has been reported involving rhabdomyolysis, renal failure, and pulmonary and hepatic injury [75–77, 81].

2.2.4 Management

There is significant overlap in the management of poisoning by amphetamines and methylphenidate. Please refer to Sect. 2.1.4 for review of the management of methylphenidate poisoning.

2.3 Modafinil

Owing to its association with Stevens-Johnson syndrome in children, although rare, modafinil is not US FDA approved for treatment of ADHD. It has been shown to improve ADHD signs and symptoms and has been used as an off-label pharmaceutical for this diagnosis in both adults and children [82, 83].

2.3.1 Pharmacokinetics

Modafinil is well absorbed orally, with peak plasma concentrations at 2–4 h [84–86]. Food delays the peak onset of modafinil by approximately 1 h [87]. Modafinil consists of two enantiomers with different pharmacokinetics. The l-isomer has a half-life three times longer than the d-isomer, and, at steady state, exists in a ratio of 3:1 (l-isomer to d-isomer) [86]. The volume of distribution is greater than that of total body water, 0.9 L/kg [86]. Modafinil is ~90 % hepatically metabolized, with primary excretion by renal route; less than 10 % is excreted unchanged [86]. Urine pH has no effect on elimination [87]. Some metabolism is through the CYP isoenzyme pathways, primarily CYP3A4, but some effects are noted on pathways CYP2C19, CYP2C9, CYP2B6, and CYP1A2 [87]. Modafinil may therefore influence drugs metabolized through these pathways (e.g. diazepam, phenytoin, tricyclic antidepressants, and selective serotonin reuptake inhibitors) [87]. The half-life (primarily noted of the l-isomer) is 12–15 h [88].

2.3.2 Mechanism of Toxicity

The mechanism of action of modafinil is complex and not fully understood. It is known to cause an increase in extracellular concentrations of dopamine, norepinephrine, and serotonin in the neocortex [89]. Modafinil decreases gamma-aminobutyric acid (GABA) release and increases glutamate release in the hippocampus and hypothalamus. Stimulation of hypocretin neurons increases the release of histamine [90]. It has been shown to bind to and inhibit DAT and NET at clinically relevant doses but appears to be selective of the hypothalamus-based wakefulness circuits as opposed to amphetamines, which produce diffuse neuron activation [91]. The dyskinesias seen with modafinil overdose suggest a dopaminergic role in the clinical toxidrome [90]. Modafinil has been shown to potentiate norepinephrine neurotransmission and these effects appear to be responsible for the adrenergic receptor-mediated effects [89–91].

2.3.3 Overdose

Overdose with modafinil is generally of moderate severity, with reported ingestions of doses up to 8 g (20 times maximum recommended daily dose) [91–93]. No fatalities from ingestions of modafinil have been reported. The clinical toxidrome involves primarily neurological and cardiovascular effects. The most common neurological effects include increased anxiety, agitation, headache, dizziness, insomnia, tremors, and dystonia. Less common effects have been hallucinations, delirium, dysarthria, and

numbness [92, 93]. A seizure after overdose was reported in one woman with a pre-existing seizure disorder who was non-compliant with her seizure medication [92]. The cardiovascular effects after overdose include sinus tachycardia, chest pain, palpitations, and hypertension. One overdose reported a mild increase in corrected QT interval (QTc) duration without tachycardia, but this has not been reported elsewhere [90]. Nausea, vomiting, abdominal pain, or diarrhea has been reported after overdose [90, 92, 93]. Clinical effects generally resolve in 12–24 h [92, 93].

Modafinil toxicity is a clinical diagnosis. Serum modafinil concentrations are rarely available, and therefore of limited clinical usefulness and are not recommended unless needed for medico-legal circumstances.

2.3.4 Management

There is significant overlap in the management of poisoning by amphetamines and modafinil, and differences are highlighted below. Please refer to Sect. 2.1.4 for review of the management of modafinil poisoning.

The management of modafinil overdose is largely supportive, with a focus on sedation, and control of dyskinesias and blood pressure.

Dystonia and movement disorders may occur in the absence of other systemic effects such as agitation or tachycardia. While some movement disorders may resolve spontaneously, treatment with diphenhydramine or benzatropine may be helpful.

Hypertension requiring intervention is rare (<10 %) but has been successfully managed with beta-adrenergic antagonists such as labetalol [92, 93].

Antiemetics may be helpful for control of nausea and vomiting.

3 Non-Stimulant Drugs

3.1 Atomoxetine

3.1.1 Pharmacokinetics

Well absorbed orally, the bioavailability of atomoxetine varies depending on first-pass effects; the range may be from 63 to 94 % [94]. Time to peak plasma concentration with oral administration is between 1 and 2 h [95]. Administration with food delays the time to peak plasma concentrations by 3 h, but does not affect the overall extent of oral absorption [94]. Atomoxetine distributes in total body water, with a volume of distribution of 0.83 L/kg after intravenous administration [94]. Metabolism of atomoxetine is through the CYP isoenzyme pathway, primarily CYP2D6 [96]. There is inter-patient variability based on isoenzyme efficiency that may lead to higher peak plasma concentrations, higher bioavailability, and slower elimination in a small percentage of individuals who are poor metabolizers (PMs). The half-life ranges from 5.2 h in normal subjects to 21.6 h in PMs [97]. Only a small percentage of atomoxetine is excreted as unchanged drug [94].

3.1.2 Mechanism of Toxicity

Atomoxetine is a selective presynaptic NET inhibitor [97]. It has no affinity for post-synaptic noradrenergic receptors and no reported effects on dopamine or serotonin [98]. The mechanism of toxicity is believed to be excessive synaptic norepinephrine concentrations. Excessive noradrenergic-mediated sympathomimetic syndrome may include tachycardia and hypertension.

3.1.3 Overdose

The clinical presentation after overdose with atomoxetine has generally been mild [99, 100]. The primary effects have been drowsiness (most common effect in children), agitation, hyperactivity, GI upset, tremor, hyperreflexia, tachycardia hypertension, and seizure [99–104]. Combination of atomoxetine with other psychoactive substances such as venlafaxine or clonidine may increase the risk of dyskinesias and toxicity [103, 104]. Neurological symptoms are usually preceded by tachycardia [100]. Duration of symptoms has generally been short, with complete resolution of symptoms after overdose in less than 24 h [99–102]. One massive overdose of 2.8 g of atomoxetine reported a mild increase in QRS duration, suggesting a possible sodium channel blockade, but this has not been reported elsewhere [101].

3.1.4 Management

The management of atomoxetine overdose is largely supportive, with a focus on sedation, and control of dyskinesias and seizures. The role of GI decontamination is limited in atomoxetine overdose. AC is expected to bind to atomoxetine, and some advocate its use if the patient presents early after the overdose (<1–2 h); however, many patients do not present in this time frame [51, 52]. Additionally, use of AC should be avoided in patients with significant risk of aspiration in whom the airway is not protected, such as those with mental status changes (CNS depression or significant agitation), or those whose clinical condition is expected to rapidly deteriorate or mandate large doses of benzodiazepines for sedation. If used, a dose of 50 g AC in adults or 1 g/kg in children is recommended.

Nausea and vomiting is common and may be controlled with antiemetics.

Intravenous benzodiazepines are first-line agents after atomoxetine overdose for agitation and seizures. Doses should be titrated to response, beginning with low doses and advancing up judiciously. Dyskinesias have resolved with intravenous benzodiazepine and/or discontinuance of the atomoxetine.

The most common dysrhythmia seen is a sinus tachycardia, which alone usually does not require intervention.

3.2 Clonidine

3.2.1 Pharmacokinetics

Clonidine is well absorbed orally, with oral bioavailability ranging from 75 to 90 % within 30–60 min; pharmacokinetics may be altered with chronic administration [105–107]. Peak plasma concentrations are reached in 1–3 h, and the terminal half-life averages 9 h [108].

Clonidine is lipophilic and readily passes the blood-brain barrier; its volume of distribution is 2.1–4 L/kg. Up to 50 % of a dose of the drug is hepatically metabolized, yielding no significant active metabolites, and 40–60 % is eliminated unchanged in the urine [109, 110]. In individuals with normal renal function, the plasma half-life is between 7.5–10.8 h and up to 40 h in those with renal dysfunction [111].

3.2.2 Mechanism of Toxicity

Clonidine is a synthetic imidazole derivative with agonist activity at both central and peripheral alpha adrenergic receptors [112]. Activation of post-synaptic alpha-adrenergic receptors in the cardiovascular center of the medulla results in reduced sympathetic outflow with decreased heart rate, cardiac output, peripheral resistance, and blood pressure [113, 114]. Alpha-adrenergic receptor activation in the locus coeruleus produces miosis, and CNS and respiratory depression reminiscent of opioid intoxication [115]. Alpha-2 adrenergic receptor impairment of the release of glutamate from spinal interneurons and inhibition of facilitatory coeruleospinal pathways produces hypotonia and skeletal muscle relaxation. Central alpha-adrenergic activity usually predominates; however, activation of peripheral alpha-adrenergic receptors in the vasculature has produced paradoxical hypertension [115, 117].

3.2.3 Clinical Presentation

The primary clinical syndrome involves prominent neurological and cardiovascular effects, with the most commonly reported features of depressed sensorium, bradycardia, and hypotension [118–122]. The most common neurological effects include lethargy, coma, ataxia, miosis, depressed reflexes, and hypotonia [119–122]. Hypothermia can be seen [123–125]. In cases with prominent CNS depression, pallor, respiratory depression, and apnea are sometimes seen [123, 124, 126]. In rare cases, hypoglycemia can be seen after overdose and following administration for diagnostic testing, such as testing for growth hormone deficiency, adding to the list of reasons why hypoglycemia should be excluded in all patients with altered mental status [127, 128]. Seizures have been reported and may be secondary to hypoglycemia [127]. Other uncommon effects include irritability, hyperventilation, and mydriasis [120, 129, 130]. The most common cardiovascular effects include bradycardia and hypotension [119, 120]. It is usually a sinus bradycardia; however, sinus dysrhythmia and atrioventricular block has been reported [11, 131]. While clonidine is an anti-hypertensive medication, a paradoxical hypertension may occur with overdose [116, 117, 130, 132]. An initial hypertension on presentation may progress to hypotension [133].

3.2.4 Management

The management of clonidine overdose is largely supportive, with a focus on support of blood pressure and respirations. Outcome following overdose is generally excellent with supportive care, with full recovery reported after 1,000-fold dosing errors [130, 133]. Death is infrequent, even with massive ingestions [122].

The role of GI decontamination is limited in clonidine overdose. AC is expected to bind to clonidine and is recommended if the patient presents early after the overdose (<1–2 h) with large intentional ingestions. Additionally onset of neurological effects such as prominent CNS and respiratory depression may make it difficult to administer.

Sinus bradycardia without hypotension or symptoms of peripheral hypoperfusion may not require intervention. Intravenous crystalloid boluses are recommended as a first-line treatment for hypotension [121]. Atropine may improve heart rate, with resultant increases in cardiac output and blood pressure. Patients with severe or persistent bradycardia or hypotension may benefit from vasopressors, such as dopamine [123, 124, 134, 135]. Alpha-adrenergic antagonists, such as tolazoline and yohimbine, have been used in clonidine overdose but results have been mixed [121, 136]. Alpha-antagonists carry a risk of paradoxical peripheral vasoconstriction and are not recommended [121, 136]. A direct vasodilator, such as nitroprusside, is recommended in rare cases of hypertension requiring intervention [137, 138]. External warming may be required for hypothermia.

Respiratory depression and apnea may require intubation and ventilator support. Naloxone may reverse CNS depression and respiratory depression, but responses have

been inconsistent [139–141]. Because the risks of naloxone use are minimal, a trial of this medication should be considered.

Seizures are quite rare. Seizures in the presence of hypoglycemia should initially be treated with intravenous glucose. In the absence of hypoglycemia, seizures should be treated with intravenous benzodiazepines.

3.3 Guanfacine

3.3.1 Pharmacokinetics

Guanfacine is well absorbed orally, reaching peak plasma concentrations within 1.5–4 h for immediate-release preparations and 5 h with extended-release formulations [142–145]. High-fat food alters the rate and extent of absorption of extended-release preparations, increasing peak plasma concentrations [146]. Guanfacine is hepatically metabolized, with the kidneys the primary route of elimination [142]. Metabolism is through the CYP isoenzyme CYP3A4 and guanfacine is not affected by other major CYP isoenzymes [146]. The half-life is approximately 17 h, and renal impairment does not significantly affect guanfacine levels [147, 148].

3.3.2 Mechanism of Toxicity

Guanfacine is a synthetic imidazole derivative, with both central and peripheral alpha-adrenergic agonist actions [149, 150]. Activation of post-synaptic alpha-adrenoreceptors in the cardiovascular center of the medulla results in reduced sympathetic outflow, with decreased heart rate, cardiac output, peripheral resistance, and blood pressure. Alpha-adrenergic receptor activation in the locus coeruleus produces miosis, and CNS and respiratory depression reminiscent of opioid intoxication [115]. Central alpha-adrenergic activity usually predominates; however, activation of peripheral alpha-adrenergic receptors in the vasculature has produced paradoxical hypertension [150, 151]. Peak hypotensive effects may be delayed and may not occur for 12–18 h post-ingestion, probably due to slow release of drug from certain tissue stores [6, 151, 153, 154]. Rebound hypertension and tachycardia are thought to be less severe and frequent than that seen with clonidine; however, mild increases in these parameters have been noted upon rapid cessation of this medication, and one case of hypertensive crisis with subsequent hypertensive encephalopathy has been reported [146, 155–161].

3.3.3 Clinical Presentation

The clinical syndrome after overdose of guanfacine may be mixed, depending on central or peripheral alpha-adrenergic receptor effects. Initial clinical effects may be drowsiness, lethargy, dry mouth, and diaphoresis [151, 153]. While CNS depression is commonly reported, respiratory depression has not been reported, even with massive ingestion [151, 153, 162]. Cardiovascular effects may depend on time post-ingestion and may present as hypotension or hypertension [151–153, 162]. Hypertension, if seen, usually presents early and may persist for up to 17 h [151, 152]. Hypotension is more common after overdose [6, 162]. However, onset of hypotension may be delayed and may follow an initial hypertensive period [151]. A persistent orthostatic hypotension associated with syncopal episodes may be seen lasting up to 48–60 h [151, 153]. Similar persistent orthostatic hypotension has been seen with other imidazole derivatives [163]. Bradycardia may be seen in the presence of hypertension or hypotension [6, 151, 153, 162].

3.3.4 Management

The management of guanfacine overdose is largely supportive, with a focus on support of blood pressure.

GI decontamination with AC can be performed following guanfacine ingestion, with patient selection and dose identical to that following clonidine ingestion and discussed in Sect. 3.2.4.

Hypertension may be severe [153, 155]. A direct vasodilator, such as nitroprusside or nicardipine, is recommended in cases of hypertension requiring intervention [153].

In the presence of severe hypertension and mental status change, it may be warranted to investigate for encephalopathic changes using computed tomography (CT) or magnetic resonance imaging (MRI) of the brain [155].

Hypotension should be treated in a manner similar to clonidine-induced hypotension, with intravenous crystalloid recommended as first-line therapy. Sinus bradycardia without hypotension may not require intervention.

Because peak hypotensive effects can be delayed, an extended monitoring period is advocated by some, although no consensus exists [151]. A monitoring period of 24 h was suggested in one report describing a 2-year-old child following an exploratory guanfacine ingestion and delay of peak hypotensive effect for 16 h; however, this child exhibited lethargy within 35 min of ingestion [154]. Most reports suggest that peak hypotensive effects occur within 12–18 h; however, delays of 19.5 and 30 h were seen in two case reports; both patients recovered well with supportive care or brief use of vasopressors and neither had permanent sequelae or death [6, 151, 153, 154].

4 Conclusion

Overdose of ADHD medications can produce major morbidity, necessitating rapid institution of life-saving

treatments, such as respiratory and cardiovascular support, with resultant prolonged hospital lengths of stay. Despite this, fatalities are rare with appropriate treatment.

The management of overdose with stimulant ADHD medication is based primarily on reducing the sympathomimetic drive. The primary organ systems affected are the CNS and cardiovascular systems, with potential secondary multi-organ injury if the sympathomimetic overdrive is uncontrolled. In the case of the amphetamines and methylphenidate, benzodiazepines are first-line agents after overdose for agitation, movement disorders, seizures, tachycardia, and hypertension. Second-line therapies may include antipsychotics such as ziprasidone or haloperidol, central alpha-adrenergic agonists, such as dexmedetomidine, or propofol. Prompt control of seizures, agitation, and hypertension may reduce the risk of secondary multi-organ involvement.

The primary concern after overdose of non-stimulant ADHD medications is control of blood pressure, movement disorders and, although rare, seizures. Though CNS depression is common, these patients are often safely managed with supportive care alone.

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